REMARKS

The Examiner has made numerous rejections and we list them here in the order in which they are addressed.

I. Rejections Under 35 USC § 112

A. Claims 28-31, 33, 35-36, 40-44, 46, 50, and 55-58 are rejected under 35 USC § 112 ¶ 1 as allegedly containing subject matter that is not described in the specification.

B. Claims 28-31, 33, 35-36, 40-44, 46, 50, 55-58 are rejected under 35 USC § 112 ¶ 1 as allegedly failing to comply with the enablement requirement.

C. Claims 28-31, 33, 35-36, 40-44, 50, 55-58 are rejected under 35 USC § 112 ¶ 2 as allegedly being indefinite.

II. Rejections Under 35 USC § 102

A. Claims 28, 31, 33, 35-36, 40-44, 46, 50, 56, and 58 are rejected under 35 USC § 102(b) as allegedly being anticipated by LeBonneic et al., *JBC* 266:13796-13803 (1991).

B. Claims 28-31, 33, 35-36, 40-44, 46, 50, 56, and 58 are rejected under 35 USC § 102(b) as allegedly being anticipated by Wu et al., *Proc. Natl. Acad. Sci USA*, 94:13654-13660 (1997)(Wu I).

C. Claims 28-31, 33, 35-36, 40-44, 46, 50, 56, and 58 are rejected under 35 USC § 102(b) as allegedly being anticipated by Cote et al. *United States Patent No. 5,510,248* (Filed: 1993) as evidenced by Deguchi et al., *Biochem J*, 321:729-735 (1997).

D. Claims 28-31, 33, 35-36, 40-44, 46, and 50 are rejected under 35 USC § 102(b) as being allegedly anticipated by Wu et al., *Thrombosis Research*, 96:91-98 (1999)(Wu II) as evidenced by Wu I.

E. Claims 38-30, 33, 35-36, 40-42, 44, 46, and 50 are rejected under 35 USC § 102(b) as allegedly being anticipated by Wu II.

F. Claims 28, 33, 36, 40, 42, 44, 50 and 57 are rejected under 35 USC § 102(b) as allegedly being anticipated by Seegers et al., *Blood*,

5:421-433 (1950) as evidenced by NCBI BLAST search for bovine prothrombin.

G. Claims 28, 33, 36, 40, 42, 44, 50, and 57 are rejected under 35 USC § 102(b) as allegedly being anticipated by Vogel et al., *Biochemistry*, 15: 3265-3269 (1976).

H. Claims 28, 33, 36, 40, 42, 44, 50, and 57 are rejected under 35 USC § 102(b) as allegedly being anticipated by Landaburu et al., *Am J. Physiol.*, 193:169-180 (1958).

III. Claims 40, 50, and 55 are rejected under 35 USC § 103(a) as allegedly being unpatentable over Morcol et al., *USP 6,183,803* (Filed: 1999).

I The Claims Adhere To 35 U.S.C. § 112

A. The Claims Are Described In The Specification

The Examiner has rejected Claims 28-31, 33, 35-36, 40-44, 46, 50, and 55-58 under 35 USC § 112 ¶ 1 as allegedly containing subject matter that is not described in the specification. In framing this rejection, the Examiner has admitted that the Applicant's specification teaches specific amino acid residues that may result in a variety of post-translational modifications. *Office Action pg 4-5.* However, the Examiner believes that the specification allegedly does not describe any relationship between post-translational modifications and changes in polypeptide activities:

> While the specification provides general guidance on these post-translational modifications and generally indicates some of the biological effects that would result from changes in post-translational modification, the specification does not provide the correlation between the structures of domains or regions of prothrombin/thrombin and the effect(s) these changes have on prothrombin/ thrombin biological activity, such that an artisan would know what structures of prothrombin/thrombin to maintain that specific activity of prothrombin/thrombin to a specific reagent would maintained or predictably changed.

Office Action pg 5 ln 17 – pg 6 ln 2. The Applicant's disagree. The specification contains published references (summarizing the state of the art and incorporated by reference) authored by those having ordinary skill in the art describing that a post-translational modification, such as γ-carboxylation, results in an active prothrombin polypeptide.

In fact, the Examiner admits this by stating that "The specification teaches that in particular for humans, it appears that complete carboxylation is required for activation and conversion of prothrombin to thrombin." *Office Action pg 5.* Nonetheless, without acquiescing to the Examiner's argument but to further the prosecution, and hereby expressly reserving the right to prosecute the original (or similar) claims, Claim 40 has been amended to specify a "completely γ-carboxylated Gla domain". *See Applicants' Specification pg 3 ln 18-21.* Claims 42, 44, 46, 50, 56, 57, & 58 are concomitantly amended to maintain proper antecedent basis relationships. Further, Applicants have concomitantly canceled Claims 28-31, 33, 35-36, 41, 43, & 55. These amendments are made not to acquiesce to the Examiner's argument but only to further the Applicants' business interests, better define one embodiment and expedite the prosecution of this application.

The Examiner is requested to note new Claim 59 describing a transgenic organism based upon the above described composition.

The Applicants, therefore, respectfully request that the Examiner withdraw the present rejection.

B. The Claims Are Enabled

The Examiner states that Claims 28-31, 33, 35-36, 40-44, 46, 50, 55-58 are rejected under 35 USC § 112 ¶ 1 as allegedly failing to comply with the enablement requirement. The Examiner summarizes this rejection by stating that "The primary issue that is being raised in the enablement rejection is similar to that of the written description ..." *Office Action, pg 8.* The Applicants disagree for the same reasons presented above in rebuttal of the Examiner's written description rejection, and consequently rely on those arguments and claim modifications.

The Applicants, therefore, respectfully request that the Examiner withdraw the present rejection.

C. The Claims Are Definite

1. Claims 28, 40, and 55 Properly Recite "transgenic polypeptide"

The Examiner asserts a "dictionary.com" definition of "transgenic" to support an argument that the term must directly modify an organism:

> According to dictionary.com, transgenic means, "Of, relating to, **or being** an organism whose genome has been altered by the transfer of a gene or gnees from another species or breed: *transgenic mice; transgenic plants*," and <u>is used to describe an organism</u>, and not a polypeptide.

Office Action pg 11 [emphasis added]. The Applicants disagree. The Examiner is reminded that the cited dictionary.com definition for "transgenic" clearly states "Of, relating to, or being an organism. The modification of the term "organism" is presented in the alternative, not exclusively as the Examiner apparently believes. The Examiner should note that "dictionary.com" defines the term "relating or related" as follows:

> *v.* re·lat·ed, re·lat·ing, re·lates
> *v. tr.*
> [...]
> 2. To bring into or link in logical or natural association. ...
> 3. To establish or demonstrate a connection between.

The American Heritage® Dictionary of the English Language, Fourth Edition Copyright © 2000 by Houghton Mifflin Company. Published by Houghton Mifflin Company. Since a polypeptide has "an established connection" and is linked in "a natural association" with the organism that produces the polypeptide, the claim term "transgenic polypeptide" is properly used.

The Examiner is reminded that "The patent law 'allows the inventor to be his own lexicographer,' " *Loctite Corp. v. Ultraseal Ltd.*, 781 F.2d 861, 867, 228 USPQ 90, 93 (Fed. Cir. 1985) (*quoting Autogiro Co. of America v. United States*, 384 F.2d 391, 397, 155 USPQ 697, 702 (Ct. Cl. 1976)) and that the term "transgenic polypeptide" is not a phrase that would be repugnant to those having ordinary skill in the art.

The Applicants respectfully request that the Examiner withdraw the present rejection.

2. Claims 28, 33, 36, 40, 44, and 55 Properly Recite "region"

The Examiner apparently believes that the term "region" is unclear "... because there are no upper and lower limits as to what comprises a "region." *Office Action, pg 11 ln 22 – pg 12 ln 1.* The Applicants disagree. Nonetheless, without acquiescing to the Examiner's argument but to further the prosecution, and hereby expressly reserving the right to prosecute the original (or similar) claims, Applicants have amended Claims 40 and 44 to recite a first or second "amino acid sequence" instead of a "region". The Examiner is reminded that Claims 28, 33, 36, and 55 were canceled above for other reasons. The Applicant has also modified the associated dependent claims to maintain a proper antecedent basis. These amendments are made not to acquiesce to the Examiner's argument but only to further the Applicants' business interests, better define one embodiment and expedite the prosecution of this application.

The Applicants respectfully request that the Examiner withdraw the present rejection.

3. Claims 28, 33, 36, 40, 44, and 55 Properly Recite "identical"

The Examiner apparently believes that ".. it is unclear if "identical" refers to the amino acid and/or the location of the amino acid in the protein". *Office Action pg 12 ln 6-7.* The Applicants disagree because one skilled in the art would certainly understand that the context unmistakably refers to the identity of the amino acids.

Nonetheless, without acquiescing to the Examiner's argument but to further the prosecution, and hereby expressly reserving the right to prosecute the original (or similar) claims, Applicants have amended Claims 40 and 44 to clarify that the term "identical" refers to an "amino acid sequence". The Examiner is reminded that Claims 28, 33, 36, and 55 were canceled above for other reasons. These amendments are made not to acquiesce to the Examiner's argument but only to further the Applicants' business interests, better define one embodiment and expedite the prosecution of this application.

The Applicants respectfully request that the Examiner withdraw the present rejection.

II. The Claims Are Not Anticipated

As the Examiner is well aware, a single reference must disclose each limitation of a claim in order for that reference to anticipate the claim. *Atlas Powder Co. v. E.I. du Pont De Nemours & Co.*, 224 U.S.P.Q. 409, 411 (Fed. Cir. 1984). This criterion is not met with any of the cited references discussed below.

At the outset, the Applicants note that the Examiner is attempting to reject the presently claimed embodiments upon a "product by process" theory. The Applicants disagree with the Examiner's logic and provide below a legal explanation of why the Examiner's approach is inappropriate in the present context. This analysis is hereby incorporated into each specific rejection listed below.

In general, the Examiner has cited references that provide teachings of recombinant prothrombin expression from *in vitro* cell lines (i.e., not *in vivo* organisms) or simply naturally secreted prothrombin isolated from blood. The Examiner then invokes the "product by process" doctrine by way of *In re Thorpe,* 227 USPQ 964 (Fed. Cir. 1985) to conclude that a recombinant transgenic prothrombin is anticipated by any recombinant prothrombin because the "...claim comprises an embodiment that the polypeptide be produced ... regardless of how it was made ...".

In re Thorpe provides a holding that is relevant only to the patentability of "product by process claims', not the patentability of "composition claims". The

Examiner is reminded that the Applicants' rejected embodiments are "composition claims". Consequently, any legal conclusions made in *In re Thorpe* are not applicable to these composition claims.

The Applicants, therefore, respectfully request the Examiner withdraw the present rejection.

A. Le Bonniec et al. Does Not Anticipate The Claims

The Examiner states that "LeBonniec et al. teach that the expression vectors were introduced to BHJ-21 (baby hamster kidney cells) ..." that express recombinant prothrombin. *Office Action pg. 13.* The Applicants disagree because Le Bonniec et al. does not teach a completely γ-carboxylated recombinant prothrombin and admits that "... we cannot conclude that all of the 10 first glutamic residues are modified by the BHK-21 cells." *See, Le Bonniec et al. 13799 lhc*

The Applicants' respectfully request that the Examiner withdraw the present rejection.

B. Wu I Does Not Anticipate The Claims

The Examiner states that "... chimeric cDNAs with the propeptide/Gla domains, kringle domain, and serine protease domains ... [were] ... expressed in both warfarin-treated HEK293 cells and HepG2 cells ..." thereby allegedly anticipating the Applicants' claimed embodiment. *Office Action pg. 14.* The Applicants disagree because the Examiner admits that a transgenic polypeptide is linked in a natural association with a transgenic organism (*supra*). Wu I does not teach the expression of any polypeptide in an organism.

The Applicants' respectfully request that the Examiner withdraw the present rejection.

C. Cote et al. As Evidenced By Deguchi et al. Do Not Anticipate The Claims

The Examiner states that "Cote et al. teach that wild type recombinant human prothrombin was expressed using the pNUT expression vector and BHK (baby hamster kidney cells ...[referring to Example 2 col 11 & 12]" thereby allegedly anticipating the Applicants' claimed embodiment. *Office Action pg 16.* The Applicants disagree because the Examiner has apparently not completely read Cote et al. The Applicants present below excerpts from Cote's Example 2 showing that the Examiner has ignored that Cote et al. discusses recombinant prothrombin that is not completely γ-carboxylated:

> The expression of wild type recombinant human prothrombin using pNUT and BHK cells has been described in detail (Le Bonniec, B.F., et al., J. Biol. Chem., 266:13796-13803, 1991)[1] ...

and,

> BHK lines have been obtained that express much higher levels of recombinant prothrombin ... however, incomplete activation was observed consistent with under γ-carboxylation of the recombinant protein.

Deguchi et al. does not offer any teaching related to recombinant prothrombin and consequently has no merit to evidence Cote et al.

The Applicants' respectfully request that the Examiner withdraw the present rejection.

D. Wu II As Evidenced By Wu I Do Not Anticipate The Claims

The Examiner states that "Wu and Suttie teach that rat prothrombin (rFII) was expressed in H-35 (hepatoma) cells in the presence of tunicamycin" thereby allegedly anticipating the Applicants' claimed embodiments. *Office Action pg 18.* The Applicants disagree because the Examiner admits that a transgenic polypeptide is linked in a natural association with a transgenic organism (*supra*). Neither Wu I nor Wu II teach the expression of any polypeptide in an organism.

The Applicants' respectfully request that the Examiner withdraw the present rejection.

E. Wu II Does Not Anticipate The Claims

The Examiner states that "Wu and Suttie teach that there are differences in glycosylation patterns and human and rat prothrombin ..." thereby allegedly anticipating the Applicants' claimed embodiments. *Office Action pg 19.* The Applicants disagree because the Examiner admits that a transgenic polypeptide is linked in a natural association with a transgenic organism (*supra*). Wu II does not teach the expression of any polypeptide in an organism.

The Applicants' respectfully request that the Examiner withdraw the present rejection.

F. Seegers et al. Does Not Anticipate The Claims

The Examiner states that "Seegers et al. teach how to prepare prothrombin" thereby allegedly anticipating the Applicants' claimed embodiments. *Office Action pg 19.* The Applicants disagree because Seegers et al. does not teach any recombinant prothrombin.

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[1] This reference was shown above as admitting that a completely γ-carboxylated prothrombin was not achieved.

The Applicants' respectfully request that the Examiner withdraw the present rejection.

G. Vogel et al. Does Not Anticipate The Claims

The Examiner states that "Vogel et al. teach that bovine prothrombin activation reactions were performed under ambient conditions ..." thereby allegedly anticipating the Applicants' claimed embodiments. *Office Action pg 22.* The Applicants disagree because Vogel et al. does not teach any recombinant prothrombin.

The Applicants' respectfully request that the Examiner withdraw the present rejection.

H. Landaburu et al. Do Not Anticipate The Claims

The Examiner states that "Landaburu ... teach that in experiments with purified bovine biothrombin, it was found that strong solutions of sodium citrate or protamine sulfate ... depress the esterase activity and leave the clotting power unaltered." *Office Action pg 22-23* thereby allegedly anticipating the Applicants' claimed embodiments. *Office Action pg 22.* The Applicants disagree because Landaburu et al. does not teach any recombinant prothrombin.

The Applicants' respectfully request that the Examiner withdraw the present rejection.

III. The Claims Are Not *Prima Facie* Obvious

The Examiner believes that Claims 40, 50, and 55 are rejected under 35 USC § 103(a) as allegedly being unpatentable over Morcol et al., *USP 6,183,803* (Filed: 1999). The Applicants disagree and argue that the Examiner has failed to make a *prima facie* case of obviousness.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the reference(s) themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488, 20 USPQ.2d 1438 (Fed. Cir. 1991); and *MPEP* § 2142; Establishing A Prima Facie Case Of Obviousness. The Examiner is reminded that if ONLY ONE of the above requirements is not met, then a *prima facie* case of obviousness does not exist. The Applicants rebut the establishment of a *prima facie* case of obviousness by the argument below.

A. Morcol et al. Does Not Provide Any Expectation Of Success

In particular, the Examiner apparently believes that:

> While Morcol and Bell does not explicitly teach recombinant prothrombin expressed in milk of a transgenic mammal, they do teach that therapeutic agents, such as prothrombin, is one protein that could be expressed in milk of transgenic mammals …

Office Action pg 24 [emphasis added]. The Applicants point out that the Examiner's choice of words that prothrombin "is one protein that could be expressed" is, without question, arguing only that the Applicants' claimed embodiments are 'obvious to try'. The Examiner is reminded that it is well settled patent law that 'obvious to try' and 'obviousness' are not equivalent:

> An invention is not obvious where the prior art gives 'no direction as to which of many possible choices is likely to be successful.

Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp., 166 F. Supp.2d 19, 36 (D. N.J. 2001), *aff'd,* 320 F.3d 1339, 65 USPQ2d 1961 (Fed. Cir. 2003); and

> A finding … that the patented invention may have been 'obvious to try' from the prior art will not invalidate it. Prior art that makes the invention only 'obvious to try' rather than 'obvious' 'gives either no indication of which parameters are critical or no direction as to which of many possible choices is likely to be successful'.

Bristol-Meyers Squibb Co. v. Ben Venue Laboratories, Inc., 246 F.3d 1368, 58 USPQ2d 1508 (Fed. Cir. 2001). The Examiner fails to meet the "expectation of success" requirement for a *prima facie* case of obviousness by simply stating that:

> There would have been a reasonable expectation of success given that Morcol and Bell provide examples of other artisans who use a transgenic mammal as a bioreactor to obtain active transgenic proteins, such as human lactoferrin, protein C, tissue-type plaminogen activator (tPA),and alpha-1-antitripsin (α1-AT).

Office Action pg 24. The Federal Circuit has ruled that explicit teachings regarding the Applicants' claimed embodiment must be present in order to provide a reasonable expectation of success, for example:

> The expectation of success must come from the prior art and explicitly predict that the process recited in the claims would work.

In re O'Farrell, 853 F.2d 894, 7 USPQ2d 1673 (Fed. Cir. 1988) [emphasis added]. The Examiner must realize that Morcol et al. merely mentions (in passing) that a transgenic organism has the potential to produce prothrombin in milk only as one of many possibilities. More to the point, Morcol et al. does not explicitly predict that any specific transgenic technique will successfully result in the production of a transgenic milk containing prothrombin as described in the Applicants' claimed embodiments.

2. Morcol et al. Does Not Teach All The Claim Limitations

Morcol et al. does not disclose any technical discussion regarding any claim limitations describing a recombinant prothrombin composition, as presented in the Applicants' claimed embodiments. For example, Morcol et al. is silent on any post-translational modifications (i.e., for example, γ-carboxylations), glutamic acid amino acids, or any amino acid sequences that are partially identical with a human prothrombin. Consequently, Morcol et al. does not teach all the claim limitations.

3. Conclusion

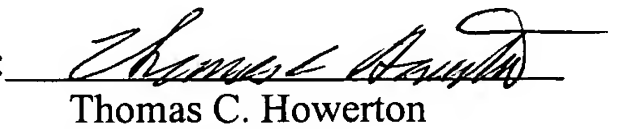
The Applicants argue that the above analysis shows that the Examiner has not made a *prima facie* case of obviousness. In particular, the cited reference (Morcol et al.) does not provide a reasonable expectation that the Applicants' claimed embodiment will work, nor does Morcol et al. teach all the Applicants' claim element.

Consequently, the Applicants respectfully request that the Examiner withdraw the present rejection.

CONCLUSION

The Applicants believe that the arguments and claim amendments set forth above traverse the Examiner's rejections and, therefore, request that all grounds for rejection be withdrawn for the reasons set above. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, the Applicants encourage the Examiner to call the undersigned collect at 617.984.0616.

Dated: June 28, 2006

By: 

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